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权利要求书3页 说明书10页 附图页数0页

[54]发明名称 制造司提多尔的方法

[57]摘要

制造司提多尔(Sertindole)的方法,包括用2,5-二氯苯甲酸的碱金属盐与N-(4-氟苯基)甘氨酸的碱金属盐在碱性水环境中在铜催化剂存在下反应制备N-(4-氟苯基)-N-(2-羧基-4-氯苯基)甘氨酸;N-(4-氟苯基)-N-(2-羧基-4-氯苯基)甘氨酸环化成相应的3-乙酸基-吲哚;3-乙酸基-吲哚还原,继而消除$H_2O$,从而得到5-氯-1-(4-氟苯基)吲哚,它与4-哌啶酮在乙酸和浓盐酸的混合物中反应;所得的5-氯-1-(4-氟苯基)-3-(1,2,3,6-四氢吡啶-4-基)吲哚还原,和这一化合物与1-(2-氯乙基)-2-咪唑啉酮反应以得到司提多尔。此外,也可使5-氯-1-(4-氟苯基)-3-(1,2,3,6-四氢吡啶-4-基)吲哚首先与1-(2-氯乙基)-2-咪唑啉酮反应,随后还原,从而得到司提多尔。此法所用反应物和溶剂适于和允许大规模生产。而且总收率很高。

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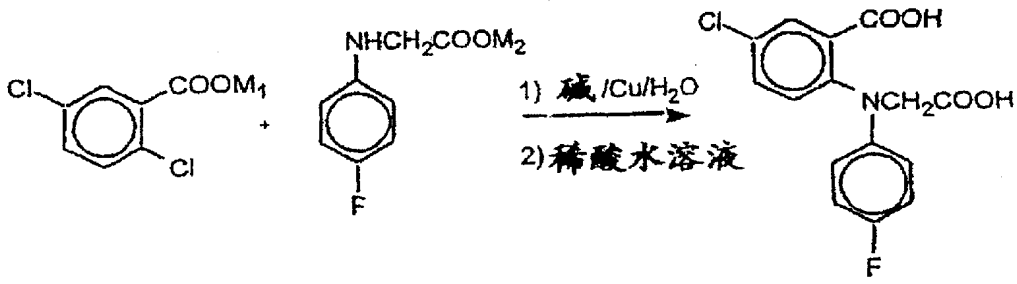
# 权 利 要 求 书

1．一种制备N－（4－氯苯基）－N－（2－羧基－4－氯苯基）甘氨酸的方法，该法包括2,5－二氯苯甲酸与N－（4－氯苯基）甘氨酸的铜催化的芳基化反应，其中2,5－二氯苯甲酸的碱金属盐和N－（4－氯苯基）甘氨酸的碱金属盐是在碱性水环境中在铜催化剂存在下按照以下反应式进行反应：




其中$M_1$和$M_2$是碱金属离子。

2．按照权利要求1的方法，其特征是反应在较高温度下进行，优选在80℃和介质的回流温度之间，特别是大约在回流温度。

3．按照权利要求1或2的方法，其特征是反应介质是水或其中加了共溶剂的水。

4．按照权利要求3的方法，其特征是水用作溶剂。

5．按照权利要求3或4的方法，其特征是用水量少于10ml/g 2,5－二氯苯甲酸，优选少于5ml/g．

6．按照权利要求5的方法，其特征是用水量小于3.5ml/g，优选少于2.5ml/g 2,5－二氯苯甲酸。

7．按照权利要求1－6的任一方法，其特征是所用碱金属盐为锂、钠或钾盐。

8．按照权利要求7的方法，其特征是反应物使用相同的盐，优选钾盐。

9．按照权利要求1－8的任一方法，其特征是所用的碱是碱金属碳酸盐，优选$Li_2CO_3$、$Na_2CO_3$或$K_2CO_3$．

10．按照权利要求9的方法，其特征是碱金属碳酸盐的碱金属是与反应物的碱金属相同。

11．按照权利要求 1 ～ 8 的任一方法，其特征是碱为碳酸钾。

12．按照权利要求 1 ～ 11 的任一方法，其特征是用碱量大于按 2,5 －二氯苯甲酸的化学计算量。

13．按照权利要求 1 ～ 12 的任一方法，其特征是催化剂为铜－青铜。

14．按照权利要求 1 － 13 的任一方法，其特征是 N －（4 －氟苯基）甘氨酸碱金属盐和 2,5 －二氯苯甲酸碱金属盐的用量比是 0.5 : 3.0，优选 1.0 : 2.5，尤其是 2.0 : 2.3 mol/mol。

15．制备 5 －氯－ 1 －（4 －氟苯基）－ 3 －（1,2,3,6 －四氢吡啶－ 4 －基）吲哚的方法，该法包括 5 －氯－ 1 －（4 －氟苯基）吲哚与 4 －哌啶酮在无机酸和乙酸的混合物中反应。

16．按照权利要求 15 的方法，其特征是所用的 4 －哌啶酮是以水合 4 －哌啶酮氢氯化物的形式。

17．按照权利要求 15 或 16 的方法，其特征是所用无机酸是磷酸、硝酸、硫酸或盐酸。

18．按照权利要求 17 的方法，其特征是所用无机酸是浓盐酸。

19．按照权利要求 15 或 16 的方法，其特征是每当量 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 1.5 当量 4 －哌啶酮。

20．按照权利要求 19 的方法，其特征是每当量 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 1.75 当量 4 －哌啶酮。

21．按照权利要求 20 的方法，其特征是每当量 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 2.0 当量 4 －哌啶酮。

22．按照权利要求 18 的方法，其特征是每克 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 2.5ml 浓盐酸。

23．按照权利要求 15 或 16 的方法，其特征是每克 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 8ml 乙酸。

24．按照权利要求 23 的方法，其特征是每克 5 －氯－ 1 －（4 －氟苯基）吲哚至少用 10ml 乙酸。

25．按照权利要求 24 的方法，其特征是每克 5 －氯－ 1 －（4 －氟苯基）吲哚用 10 ～ 14ml 乙酸。

26．按照权利要求 22 的方法，其特征是每克 5 －氯－ 1 －（4 －氟苯基）吲哚用 3.5 ～ 5ml 浓盐酸。

27．按照权利要求18的方法，其特征是乙酸和浓盐酸之比为2：1－4：1（体积/体积）。

28．制造司提多尔的方法，包括用权利要求1－14的任一方法制备N－（4－氯苯基）－N－（2－羧基－4－氯苯基）甘氨酸，和/或按照权利要求15－27的任一方法制备5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚。

29．制造司提多尔的方法包括

a） 按照权利要求1－14的任一方法，通过2,5－二氯苯甲酸的碱金属盐与N－（4－氟苯基）甘氨酸的碱金属盐在碱性水环境中在铜催化剂存在下反应制备N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸；

b） 用乙酸酐/碱金属乙酸盐，优选乙酸钠使N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸与相应的3－乙酸基－吲哚发生环化作用；

c） 3－乙酸基－吲哚还原；随后

d） 消除$H_2O$，从而得到5－氯－1－（4－氟苯基）吲哚；

e） 5－氯－1－（4－氟苯基）吲哚与4－哌啶酮按照权利要求15－27的任一方法在乙酸和浓盐酸的混合物中反应；

f） 得到的5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚还原，以得到5－氯－1－（4－氟苯基）－3－（哌啶－4－基）吲哚。

g） f）的产物与1－（2－氯乙基）－2－咪唑啉酮反应；或

h） 5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚与1－（2－氯乙基）－2－咪唑啉酮反应，随后还原产物，从而得到司提多尔。

# 说　明　书

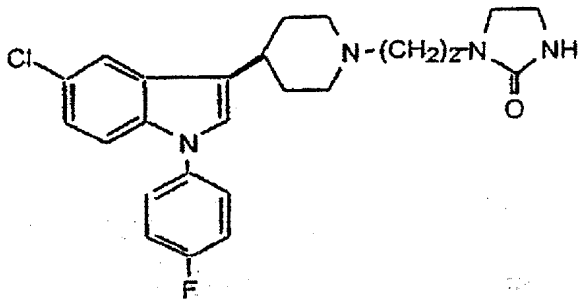
## 制造司提多尔的方法

### 发明范围

本发明涉及一种制造化合物 1 - [ 2 - [ 4 - [ 5 - 氯 - 1 - ( 4 - 氟苯基 ) - 1 - H - 吲哚 - 3 - 基] - 1 - 哌啶基] 乙基] - 2 - 咪唑啉酮的新方法，该化合物推荐的 INN 名称为司提多尔 ( sertindole )，和涉及制造该法中使用的中间体 N - ( 4 - 氟苯基 ) - N - ( 2 - 羧基 - 4 - 氯苯基 ) 甘氨酸和 5 - 氯 - 1 - ( 4 - 氟苯基 ) - 3 - ( 1, 2, 3, 6 - 四氢吡啶 - 4 - 基 ) 吲哚的新方法。

### 发明背景

司提多尔是众所周知的抗精神病药物，其通式为




该化合物已在 US 4, 710, 500 中揭示，其抗精神病活性已在 US 5, 112, 838 中描述。司提多尔是一种有效的中枢神经系统作用 5 - $HT_2$ 受体拮抗药 ( 在体内 )，而且进一步揭示出在指示焦虑、高血压、药物滥用和认识障碍的治疗效果的模型中，它是速效的。近来，有报道表明它在临床研究中的抗精神病效果。Psychopharmacology ( 1996 ) 124 : 168 - 175 。

US 4, 710, 500 报道了一类 1 - 芳基 - 3 - ( 哌嗪基 - ，四氢吡啶基或哌啶基 ) 吲哚化合物包括司提多尔。若干制备该化合物的方法一般已揭示出来，其中的有些方法可用于制备司提多尔。这些方法是:

a )适当取代的 1 - 芳基吲哚与合适的 1 - 取代的 4 - 哌啶酮反应和随后所得的四氢吡啶基化合物被还原;

b）相应的1－未取代吲哚化合物的芳基化；

c）在吲哚环2－位具有桥氧基的相应化合物的还原。

司提多尔被特别的举例说明，但是，并未给出其制备的实验程序。

Perregaard等人，J. Med. Chem., 1992，35，1092－1101中揭示了一种制备司提多尔的新方法．此法包括中间体5－氯－1－（4－氟苯基）吲哚与4－哌啶酮在三氟乙酸和乙酸的混合物中反应，得到的5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚还原，以得到5－氯－1－（4－氟苯基）－3－（哌啶－4－基）吲哚，它又与1－（2－氯乙基）－2－咪唑啉酮在甲基异丁基酮（MIBK）中及$K_2CO_3$和KI存在下反应．从相应的3－乙酸基吲哚用$NaBH_4$在甲醇中还原，随后在酸性条件下消去$H_2O$得到5－氯－1－（4－氟苯基）吲哚．3－乙酸基吲哚由N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸按下列文献程序制备。

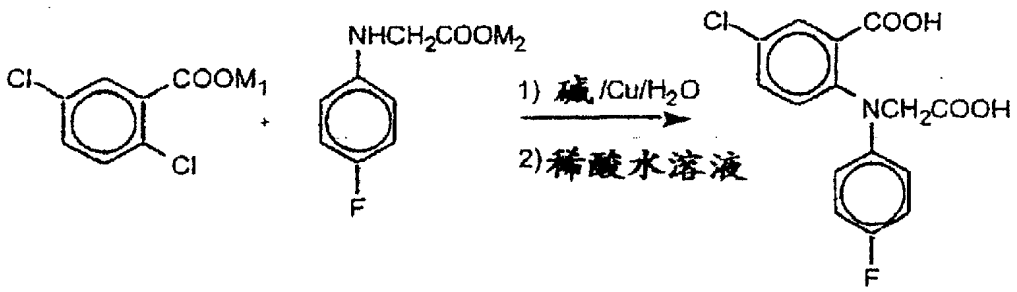
在Perregaard等人，Dansk Kemi，95，3，P.6－9中描述了制备N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸的方法．根据这一方法，该甘氨酸是通过2,5－二氯苯甲酸与N－（4－氟苯基）甘氨酸发生铜催化的反应制备的．在溶剂N－甲基吡咯烷酮（NMP）中在$K_2CO_3$存在下，应用这两种酸的钾盐．

然而，已经发现上面的方法不能以工业规模应用．总收率太低，且该方法中所使用的反应物或溶剂，由于环境和安全方面的理由，大规模使用是不适当的，且在某些情况下是不允许的．另外，由于NMP的水溶解性差，反应是慢长乏味的，而且NMP的再生是昂贵和费时的。

因而，本发明关系到一种可在工业规模生产司提多尔的新方法。

现已发现该法的主要限制性步骤是N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸的制备和5－氯－1－（4－氟苯基）吲哚与4－哌啶酮的反应。

因此，本发明提供一种制备N－（4－氟苯基）－N－（2－羧基－4－氯苯基）甘氨酸的方法，该法包括2,5－二氯苯甲酸的碱金属盐与N－（4－氟苯基）甘氨酸的碱金属盐在含水碱性环境中，在铜催化剂存在下反应，继之用含水酸处理，如下列反应式所示：

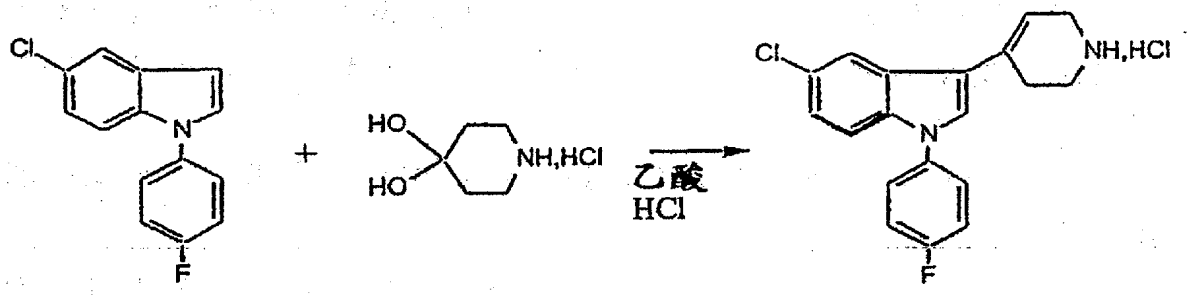



其中 $M_1$ 和 $M_2$ 是碱金属离子。

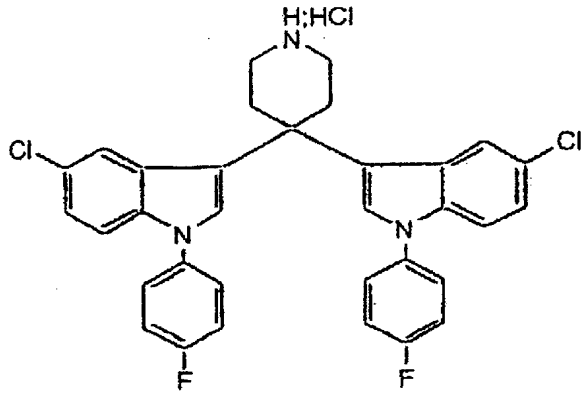
根据 Perregaard 等人， Dansk Kemi， 95，用该反应物的钾盐在 NMP 中进行反应。不过， NMP 的使用需消耗完成提取的时间，而且反应得到大量焦油状副产物。反应温度为 120 ~ 130 ℃。

通过在水环境而不是在 NMP 中进行反应，可以得到较高的产率和可忽略量的焦油状副产物。此外，操作方法也比较简单，而且水介质的应用带来很大的环境好处。最后，将反应温度降到水介质的回流温度或更低。

另一方面本发明提供一种制备 5 - 氯 - 1 - （ 4 - 氟苯基） - 3 - （ 1, 2, 3, 6 - 四氢吡啶 - 4 - 基）吲哚的新方法，该法包括 5 - 氯 - 1 - （ 4 - 氟苯基）吲哚与 4 - 哌啶酮在无机酸和乙酸的混合物中反应，如下面的反应式所示:




通过用乙酸和无机酸的混合物代替三氟乙酸 - 乙酸混合物，得到巨大的环境好处。况且，三氟乙酸很易挥发和有侵蚀性，因而不宜于大规模生产。还有，可以避免不希望有的双取代哌啶的生成:




式 I

在还有的另一方面，本发明提供一种制造司提多尔的新方法，该法包括制备 N－（4－氯苯基）－N－（2－羧基－4－氯苯基）甘氨酸，所用的反应是 2, 5－二氯苯甲酸的碱金属盐与 N－（4－氯苯基）甘氨酸的碱金属盐在碱性水溶液环境中在铜催化剂存在下发生铜催化反应和/或在其中通过反应得到 5－氯－1－（4－氯苯基）－3－（1, 2, 3, 6－四氢吡啶－4－基）吲哚，该反应包括 5－氯－1－（4－氯苯基）吲哚与 4－哌啶酮在无机酸和乙酸的混合物中反应。

2, 5－二氯苯甲酸的碱金属盐与 N－（4－氯苯基）甘氨酸的碱金属盐的反应是在较高的温度下进行，合适的是在 80 ℃和介质的回流温度之间，优选约在回流温度。

在说明书和权利要求中，术语水介质是指包括水和一种共溶剂如乙二醇加入水中作为反应介质。优选所用的水如软化水、去离子水或蒸馏水。

优选的反应物的碱金属盐是锂、钠或钾盐，应用相同的反应物盐是适宜的。最优选应用钾盐。

为了避免不需要的副反应，重要的是在反应期间生成的 HCl 要被中和。通过加入一种碱，如碱金属氢氧化物、碱金属乙酸盐、碱金属碳酸盐、碱金属碳酸氢盐、碱金属磷酸盐或碱金属柠檬酸盐使反应介质成为碱性的。优选使用碱金属碳酸盐，如 $Li_2CO_3$、$Na_2CO_3$ 或 $K_2CO_3$。反应物使用相同的碱金属是合宜的。优选的碱是碳酸钾。碱量优选大于 2, 5－二氯苯甲酸的化学计算量。另一方面，增加[ $OH^-$ ]会使 2, 5－二氯苯

甲酸水解，因而降低产量。因此，在制作过程中逐渐加碱是适合的。

催化剂可以是任何 Cu(0)－催化剂，优选铜－青铜。以催化量加入。量比并不严格，而且熟悉本技术的人很容易确定。

N－（4－氯苯基）甘氨酸的碱金属盐的量和 2,5－二氯苯甲酸碱金属盐的量之比从 0.5：3.0 是适宜的，优选 1.0：2.5，最优选 2.0：2.3 mol/mol。过量的 N－（4－氯苯基）甘氨酸可以再生。

以最小量的含水溶剂进行反应是适合的，但要在技术上是可行的。因而，通过降低溶剂量可改进收率。水量优选低于 10 ml/g 2,5－二氯苯甲酸，更优选低于 5ml/g，特别是低于 3.5ml/g，最优选低于 2.5ml/g。

反应时间不是很严格，熟悉本技术的人很容易确定。

用稀酸水溶液进行产品的后处理是很简单的，方法是将滤过的反应混合物加到稀酸中，从而沉淀出产物，用热甲苯或通过自乙醇水溶液中重结晶，可使产品进一步纯化。稀酸水溶液优选盐酸。

在 5－氯－1－（4－氯苯基）吲哚与 4－哌啶酮的反应中，所用无机酸优选磷酸、硝酸、硫酸或盐酸，如大于 30 % w/w 的 HCl 水溶液。

优选所用 4－哌啶酮为水合 4－哌啶酮的氢氯化物。

反应最好在过量水合哌啶酮氢氯化物的情况下进行。优选每当量 5－氯－1－（4－氯苯基）吲哚使用大于 1.5 当量 4－哌啶酮，更优选使用高于 1.75。使用 2.0 当量也是适宜的。

重要的是要有足够的酸存在，以使收率足够。当采用盐酸作为无机酸时，优选每克 5－氯－1－（4－氯苯基）吲哚使用至少 2.5ml 浓盐酸。最优选每克 5－氯－1－（4－氯苯基）吲哚用 3.5－5ml 浓盐酸。

乙酸的量必须足以使反应在技术上可行。每克 5－氯－1－（4－氯苯基）吲哚使用至少 8ml 乙酸是合宜的。优选每克 5－氯－1－（4－氯苯基）吲哚使用乙酸的量大于 10ml，最优选 10－14ml。乙酸和浓盐酸的比例优选 2：1－4：1 体积/体积。

把 5－氯－1－（4－氯苯基）吲哚在热乙酸中的溶剂一滴滴地加到水合吡啶酮氢氯化物中或通过在乙酸和无机酸的混合物中混合两种反应物然后回流即可方便地发生反应。

熟悉本技术的人很容易确定反应时间。

中间体可以用方便的方式处理。

得到司提多尔的进一步加工包括N－（4－氯苯基）－N－（2－羧基－4－氯苯基）甘氨酸环化为相应的3－乙酸基－吲哚，使用例如在碱金属乙酸盐（如乙酸钠）存在下的乙酸酐。然后由3－乙酸基吲哚通过还原继而消除$H_2O$得到5－氯－1－（4－氟苯基）吲哚。所得到的5－氯－1－（4－氟苯基）吲哚按上面的步骤与4－吡啶酮反应，将得到的5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚还原，以得到5－氯－1－（4－氟苯基）－3－（哌啶－4－基）吲哚，它再与1－（2－氯乙基）－2－咪唑啉酮反应，得到司提多尔。另外，5－氯－1－（4－氟苯基）－3－（1,2,3,6－四氢吡啶－4－基）吲哚可先与1－（2－氯乙基）－2－咪唑啉酮反应继而还原，从而得到司提多尔，它可以作为一种酸加成盐，例如酒石酸盐，或作为游离碱分离出来。

用作起始物的2,5－二氯苯甲酸的碱金属盐和N－（4－氟苯基）甘氨酸的碱金属盐很容易由市场购得的2,5－二氯苯甲酸和N－（4－氟苯基）甘氨酸经标准操作步骤分别制备。

用本法所得的司提多尔可以方便地以如US 5,112,838中所描述的方法配制。

实验项

实例1

N－（4－氟苯基）－N－（2－羧基苯基）甘氨酸的制备

将含有2,5－二氯苯甲酸钾（100 g，0.44 mol，1当量），N－（4－氟苯基）甘氨酸钾（190 g，0.92 mol，2.1当量），碳酸钾（36.2 g，0.26 mol，0.6当量。$CO_3^{2-}$），铜－青铜（2.8 g，0.04 mol Cu，0.1当量）和250 ml软化水的悬浮液在回流下，在$N_2$气氛下加热20.5小时，然后冷却至50 ℃。将2.5 ml水和5 g活性炭加到反应混合物中，除了铜－青铜外，该混合物是均相的。将所得混合物在搅拌下冷却1小时，过滤。滤饼用2 × 125 ml水洗涤。在强烈搅拌下将滤液浇在冰（2 L）和37 %盐酸水溶液（300 － 400 ml）的混合物上，从而将粗产物结晶成精细的晶体状黄棕色物。将悬浮液在75 － 80 ℃下搅拌30分钟，冷却至15 ~ 20 ℃，然后过滤，滤饼用500 ml水洗涤，在空气流中于50 ℃干燥过夜。

收集滤液，以备N－（4－氯苯基）甘氨酸盐的再生。

粗产物收率：113 g（80.3 %），熔点170 ~ 186 ℃。

HPCL分析：84.2 % w/w产物，10.5 % w/w 3－氯水杨酸。

上述干燥粗产物20 g通过悬浮在200 ml甲苯中并回流30分钟进一步纯化。悬浮液在搅拌下冷却至室温，然后过滤。滤饼用甲苯（20 ml）洗涤，在真空中50 ℃下干燥过夜。

收率：17.0 g，熔点190 ~ 192 ℃。纯度> 98 %，由NMP－分析测定。

实例2

N－（4－氯苯基）－N－（2－羧基苯基）甘氨酸的制备

将21.0 kg 2,5－二氯苯甲酸钾加到180 L反应器中，再加入36.0 L水。在搅拌下加热此混合物，直至所有固体基本上溶解（温度60 ~ 70 ℃），然后缓缓加入25.0 kg N－（4－氯苯基）甘氨酸钾。加热混合物，直至所有物质溶解，即在约80 ℃，将其加到7.67 kg $K_2CO_3$，582g铜－青铜和7 L水的混合物中。将复合混合物回流过夜（约15小时）并冷却至50 ℃。加入悬浮在5 L水中的1 kg活性炭，再加40 L水。混合物在冷却下搅拌1小时，在一个覆盖有过滤设备的上下真空滤器上过滤。滤饼用10 L水洗涤，并将绿色的滤液在温和加热（45 ~ 50 ℃）和搅拌下在约2小时内浇在22.5 L 37 %盐酸和30 L水的混合物上。所得混合物加热至72 ℃，冷却至25 ℃并过滤。滤饼用水（2 × 10 L）洗涤，在塔盘上于60 ℃干燥过夜。得到26.7 kg灰黄色晶体粗产物。

将得到的26.7 kg粗产物转移到200 L反应器中，加入150 L甲苯，将混合物在$N_2$覆盖下加热至回流温度（90 ℃）。然后蒸馏混合物，直至达到110 ℃温度（5 L馏出液）。加入5 L甲苯，混合物在110 ℃回流2小时，冷却至约60 ℃，在27 ℃下留存过夜。过滤混合物，滤饼用甲苯（3 × 15 L）洗涤并干燥，结果得到21.0 kg纯标题产物。

实例3

1－（4－氯苯基）－3－乙酸基－5－氯吲哚

将N－（4－氯苯基）－N－（2－羧基苯基）甘氨酸（717.1 g，

2.22 mol），乙酸钠（36.4 g，0.44 mol，0.2 当量）和乙酸酐放入装有机械搅拌和回流冷凝器的 4 L 三颈烧瓶中。

将上述悬浮液在搅拌下加热直至回流。回流反应混合物 1 小时，在冰/水浴上冷却至室温。均相悬浮液在搅拌下倒至 2 L 冰上，用浓 NaOH（约 6 L）中和，直至 pH 为 6 - 7。在中和期间温度保持约 30 ℃，这需要再加 5 ~ 6 升冰。结果产物沉淀，用过滤法分离。用 3 L 水和 2 L 正庚烷彻底清洗产物，在真空中 60 ℃下干燥过夜。

收率：600.5 g（89.1 %），熔点 109 ~ 112 ℃。

实例 4

1 -（4 - 氯苯基）- 5 - 氯吲哚

将 1 -（4 - 氯苯基）- 3 - 乙酸基 - 5 - 氯吲哚（100.0 g，0.33 mol）溶于 1000 ml EtOH 中。在紧接的一小时内，将氢硼化钠片（18.7g，1.5 当量）在回流下分批加入。反应混合物在回流下搅拌过夜，并冷至室温。加入浓 HCl（约 50 ml，直至 pH 为 1），在室温下搅拌反应混合物 1 小时。加入 200 ml 软化水，将所得悬浮液过滤。滤饼再用 50 ml 水和 10 ml EtOH 洗涤。产物在真空中于 50 ℃干燥过夜。

收率：68.4 g（84.7 %），熔点 91 ~ 93 ℃。

实例 5

5 - 氯 - 1 -（4 - 氯苯基）- 3 -（1, 2, 3, 6 - 四氢吡啶 - 4 - 基）吲哚的制备

将 5 - 氯 - 1 -（4 - 氯苯基）吲哚（6.70 kg）和水合 4 - 哌啶酮氢氯化物（8.38 kg）在 $N_2$ 覆盖下输入到 200 L 反应器中。加入乙酸（67 L），反应混合物加热至 60 ℃。在 0.5 小时内加入浓 HCl（37 %，33.5 L），然后加热混合物至回流温度（85 ℃），回流 1 小时（最终温度 95 ℃）。在冷却至 30 ℃后，加入 33.5 L 丙酮，然后进一步冷却至 25 ℃。过滤，洗涤（20 L 丙酮）和在真空中于 60 ℃下干燥，得到标题产物白色粉末，产量 8.94 kg。

实例 6

1 - [2 - [4 - [5 - 氯 - 1 - (4 - 氟苯基) - 1H - 吲哚 - 3 - 基] - 1, 2, 3, 6 - 四氢 - 1 - 吡啶基] - 乙基] - 2 - 咪唑啉酮

混合 5 - 氯 - 1 - (4 - 氟苯基) - 3 - (1, 2, 3, 6 - 四氢吡啶 - 4 - 基) 吲哚 (6.0 kg, 16.5 mol), 1 - (2 - 氯乙基) 咪唑啉酮 (3.19 kg, 1.3 当量), 碳酸钠 (无水) 和甲基异丁酮 (60 L). 反应混合物在 $N_2$ 覆盖下加热并搅拌, 直至 90 ~ 95 ℃, 并在该温度下搅拌过夜。第二天趁热过滤反应混合物。装置和滤饼再用 2.5 L 甲基异丁酮洗涤。合并的滤液放置过夜, 以使其结晶。产物在上下真空滤器上分离出来, 用 7.5 L 正庚烷洗涤, 并在真空中于 60 ℃下干燥过夜。

收率: 5.39 kg (74.3 %), 熔点 146.4 ℃.

实例 7

1 - [2 - [4 - [5 - 氯 - 1 - (4 - 氟苯基) - 1 - H - 吲哚 - 3 - 基] - 1 - 哌啶基] 乙基] - 2 - 咪唑啉酮的酒石酸盐

1 - [2 - [4 - [5 - 氯 - 1 - (4 - 氟苯基) - 1H - 吲哚 - 3 - 基] - 1, 2, 3, 6 - 四氢 - 1 - 吡啶基] 乙基] - 2 - 咪唑啉酮 (3.5 kg) 溶于乙酸 (98 ~ 100 %, 29 L), 同时加热至 40 ℃。加入活性炭, 搅拌所得悬浮液 1 小时, 放置过夜, 并过滤。滤饼用 6 L 乙酸洗涤。合并的滤液加到 50 L 被 $N_2$ 覆盖的氢化反应器中。加入 70 g $PtO_2$, 将装置密闭, 吹氮气 5 分钟。在氢气流 (2.5 L/min) 中氢化 8.25 小时。

反应混合物用氮气吹洗, 加入活性炭, 在密闭的上下真空滤器上过滤混合物。将滤液与相应的三种其它氢化的滤液混合 (总共 14.53 kg 起始物), 在真空中近 50 ℃下蒸发。用 3 × 10 L 甲苯在 50 ~ 60 ℃冲洗滤液。剩余物溶于 146 L 乙醇中, 和将 5.22 kg L - (+) 酒石酸在 16 L 软化水中的悬浮液在搅拌下加到此悬浮液中 (40 ℃)。将所得悬浮液放置过夜, 不必冷却或搅拌。在上下真空滤器上过滤结晶的酒石酸盐, 并用 15 L 乙醇洗涤。

将粗的酒石酸盐自 190 L 乙醇和 30 L 软化水中重结晶, 加热至沸腾 (约 78 ℃)。悬浮液放置过夜, 以进行结晶, 不必冷却或搅拌。第二天, 将悬浮液冷却至近 18 ℃, 过滤出酒石酸盐, 用 60 L 乙醇洗涤, 在空气

流中于 60 ℃干燥过夜.

实例 8

1 - [2 - [4 - [5 - 氯 - 1 - (4 - 氟苯基) - 1H - 吲哚 - 3 - 基] - 1 - 哌啶基]乙基] - 2 - 咪唑啉酮

将 7.96 kg 1 - [2 - [4 - [5 - 氯 - 1 - (4 - 氟苯基) - 1H - 吲哚 - 3 - 基] - 1, 2, 3, 6 - 四氢 - 1 - 吡啶基]乙基] - 2 - 咪唑啉酮的酒石酸盐悬浮在 25 L 软化水中, 加入 30 L 二氯甲烷。在搅拌下将总共 3L 27 % NaOH 溶液 ( pH = 9 ) 加到悬浮液中。搅拌该混合物 1 小时 ( pH 仍为 9 ), 然后分出二氯甲烷相。

水相再用 15 L 二氯甲烷提取。合并的二氯甲烷相用 $Na_2SO_4$ 干燥, 然后蒸发。产品用 5 L 丙酮冲洗, 加入 35 L 丙酮, 加热悬浮液至回流。结晶产物完全不溶解. 停止加热, 混合物在缓慢冷却下放置过夜。在上下真空滤器上分离出结晶产物, 再用 5 L 丙酮洗涤, 在空气流中于 60 ℃下干燥过夜.

收率: 4.90 kg ( 83.2 % ), 熔点 154.7 ℃。

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(54) Title: METHOD OF MANUFACTURING SERTINDOLE

(57) Abstract

A process of manufacturing sertindole comprising preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine, by reacting an alkalimetal salt of 2,5-dichlorobenzoic acid with an alkalimetal salt of N-(4-fluorophenyl)glycine in an aqueous, alkaline environment in the presence of a copper catalyst; cyclisation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine to the corresponding 3-acetoxy-indole; reduction of the 3-acetoxy-indole and subsequent elimination of $H_2O$ thereby obtaining 5-chloro-1-(4-fluorophenyl)indole which is reacted with 4-piperidone in a mixture of an acetic acid and concentrated HCl; reduction of the resulting 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole and reaction of this compound with 1-(2-chloroethyl)-2-imidazolidinon in order to obtain sertindole. Alternatively, 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole is first reacted with 1-(2-chloroethyl)-2-imidazolidinon followed by reduction thereby obtaining sertindole. This process uses reactants and solvents that are suitable and allowed in large scale manufacture. Furthermore good total yields are obtained.

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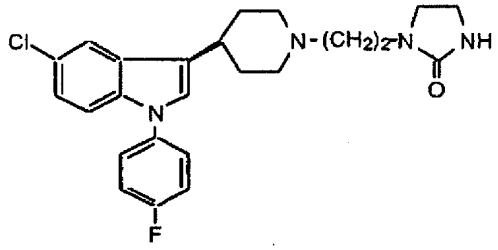
# Method of Manufacturing Sertindole

## Field of invention

The present invention relates to a new method of manufacturing the compound 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1-*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone having the recommended INN name sertindole and a new method of manufacturing the intermediates, N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine and 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole used in the method.

## Background of the invention

Sertindole is a well known antipsychotic drug having the formula




The compound was disclosed in US patent No 4,710,500 and the antipsychotic activity thereof was described in US patent No 5,112,838. Sertindole is a potent centrally acting 5-$HT_2$ receptor antagonist in vivo and has further been disclosed to be active in models indicative of effects in the treatment of anxiety, hypertension, drug abuse and cognitive disorders. Recently, it has been reported to show antipsychotic effect in clinical studies, *Psychopharmacology* (1996) 124:168-175.

US patent No 4,710,500 covered a class of 1-aryl-3-(piperazinyl-, tetrahydropyridyl or piperidyl)indole compounds including sertindole. A number of methods of preparing the compounds were generically disclosed, some of which could be used in the preparation of sertindole. The methods were:

a) reaction of a properly substituted 1-arylindole with a proper 1-substituted 4-piperidone and subsequent reduction of the resulting tetrahydropyridyl compound;
b) arylation of the corresponding 1-unsubstituted indole compound;

c) reduction of the corresponding compound having an oxo group in the 2-position of the indole ring.

Sertindole was specifically examplified, however, no experimental procedure for its preparation was given.

Perregaard et al., *J. Med. Chem*, **1992**, *35*, 1092-1101, disclosed a new method of preparing sertindole. This method comprises reaction of the intermediate 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone in a mixture of trifluoroacetic acid and acetic acid, reduction of the resulting 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole in order to obtain 5-chloro-1-(4-fluorophenyl)-3-(piperidin-4-yl)indole which in turn is reacted with 1-(2-chloroethyl)-2-imidazolidinon in the presence of $K_2CO_3$ and KI in methyl isobutyl ketone (MIBK). The 5-chloro-1-(4-fluorophenyl)indole was obtained from the corresponding 3-acetoxy-indole by $NaBH_4$ reduction in methanol and subsequent elimination of $H_2O$ under acidic conditions. The 3-acetoxy-indole was prepared from the N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine following literature procedures.

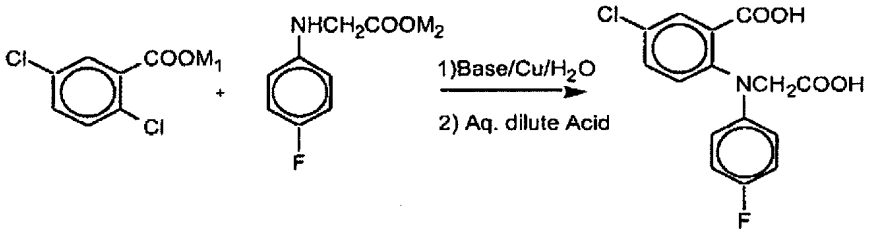
A procedure for preparing the N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine is described in Perregaard et al.,*Dansk Kemi*, **95**, *3*. p. 6-9. By this method the glycine is obtained by a copper catalyzed reaction of 2,5-dichlorobenzoic acid with N-(4-fluorophenyl)glycine. The potassium salts of the two acids are used in the presence of $K_2CO_3$ in the solvent N-methylpyrrolidone (NMP).

However, it has been found that the above processes are not useful in technical scale. The total yields are too low and the processes involve the use of reactants or solvents that are not suitable and in some cases not allowed in large scale for environmental or safety reasons. Furthermore, due to the aqueous solubility of NMP, the work-up of the reaction is tedious, and regeneration of NMP is costly and time consuming.

Consequently, the present invention relates to a new process useful in technical scale production of sertindole.

It has now been found that the main limiting steps of the process are the preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine and the reaction of 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone.

Accordingly, the present invention provides a process for the preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine comprising reaction of an alkalimetal salt of 2,5-dichlorobenzoic acid with an alkalimetal salt of N-(4-fluorophenyl)glycine in an aqueous, alkaline environment in the presence of a copper catalyst followed by treatment with an aqueous acid, as illustrated in the following reaction scheme:

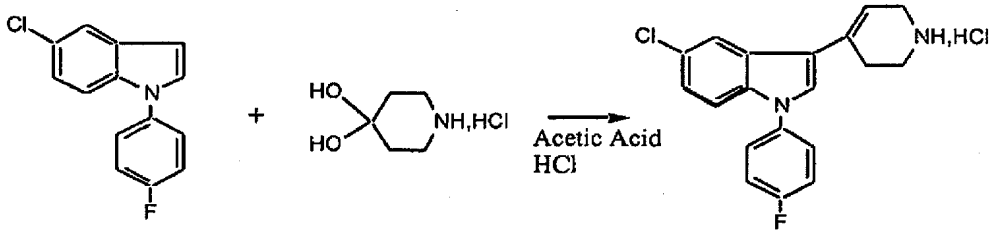



wherein $M_1$ and $M_2$ are alkali metal ions.

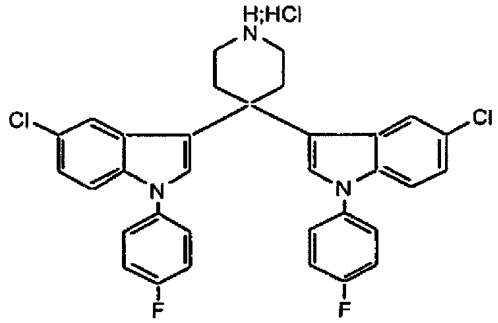
According to Perregaard et al.,*Dansk Kemi,* **95**, a reaction using the potassium salts of the reactants is carried out in NMP. However, the use of NMP necessitated a time consuming extractive work-up, and the reaction afforded substantial amounts of tarry by-products. The reaction temperature was 120-130 °C.

By carrying out the reaction in aqueous environment instead of NMP, a higher yield and only a negligible amount of tarry by-products are obtained. Furthermore, the work-up procedure is simple and the use of an aqueous medium causes substantial environmental advantages. Finally, the reaction temperature is lowered to the reflux temperature of the aquous medium or below.

In another aspect the invention provides a novel process for preparing 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole comprising reaction of the 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone in a mixture of a mineral acid and acetic acid, as illustrated in the following reaction scheme:




By using a mixture of acetic acid and a mineral acid instead of a trifluoroacetic acid - acetic acid mixture, substantial environmental advantages are obtained. Furthermore, trifluoro acetic acid is very volatile and aggressive, accordingly being undesirable for large scale production. Also, the formation of the undesired bis-substituted piperidine may be avoided:




Formula I

In yet another aspect, the invention provides a novel process of manufacturing sertindole comprising preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine by a reaction comprising a copper catalysed reaction of an alkalimetal salt of 2,5-dichlorobenzoic acid with an alkali metal salt of N-(4-fluorophenyl)glycine in an aqueous, alkaline environment in the presence of a copper catalyst and/or in which 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole is obtained by a reaction comprising reaction of the 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone in a mixture of a mineral acid and acetic acid.

The reaction of the alkalimetal salt of 2,5-dichlorobenzoic acid with the alkalimetal salt of N-(4-fluorophenyl)glycine is carried out at an elevated temperature, conveniently at a

temperature between 80 °C and the reflux temperature of the medium, preferably at about the reflux temperature.

Throughout the specification and claims the term aqueous medium is intended to include water and water to which a cosolvent such as ethyleneglycol is added as reaction medium. Preferably water such as demineralised, deionised or destilled water is used.

Preferred alkali metal salts of the reactants are the lithium, sodium or potassium salts and conveniently the same salts of the reactants are used. Most preferably the potassium salts are used.

It is important that the HCl formed during the reaction is neutralised in order to avoid undesired side reactions. The reaction medium is made alkaline by addition of a base such as an alkali metal hydroxide, alkali metal acetate, alkali metal carbonate, alkali metal hydrogen carbonate, alkali metal phosphate or alkali metal citrate. Preferably an alkali metal carbonate, such as $Li_2CO_3$, $Na_2CO_3$ or $K_2CO_3$, is used. Conveniently, the same alkali metal as included in the reactants is used. Preferably the base is potassium carbonate. The amount of base is preferably larger than the stoechiometric amount of 2,5-dichlorobenzoic acid. On the other hand, increased [$OH^-$] may cause hydrolysis of 2,5-dichlorobenzoic acid, thereby decreasing the yield. Thus, the base may conveniently be added gradually during the process.

The catalyst may be any Cu(0)-catalyst, preferably copper-bronze. It is added in catalytic amounts. The specific amount is not critical and may easily be determined by a person skilled in the art.

The ratio between the amounts of the alkali metal salt of N-(4-fluorophenyl)glycine and the alkali metal salt of 2,5-dichlorobenzoic acid is conveniently from 0.5 to 3.0, preferably 1.0 to 2.5 and most preferably 2.0 to 2.3 mol/mol. Excess N-(4-fluorophenyl)glycine may be regenerated.

The reaction is conveniently carried out in a minimal amount of aqueous solvent still technically feasible. Thus, the yield is improved by decreasing the amount of solvent. The

amount of water is preferably less than 10 mL/g 2,5-dichlorobenzoic acid, more preferably less than 5 mL/g in particular less than 3.5 mL/g, most preferably less than 2.5 mL/g.

The reaction time is not very critical and may easily be determined by a person skilled in the art.

The work-up of the product by dilute aqueous acid may be carried out simply by adding the filtered reaction mixture to the dilute acid, thereby precipitating the product. The product may be further purified with hot toluene or by recrystallisation from aqueous ethanol. The dilute aqueous acid is preferably hydrochloric acid.

In the reaction of the 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone, the mineral acid used is preferably phosphoric acid, nitric acid, sulfuric acid or hydrochloric acid, such as larger than 30% w/w aqueous HCl, in particular concentrated hydrochloric acid. By concentrated HCl is meant about 37% w/w aqueous HCl.

The 4-piperidone is preferably used as the 4-piperidone-hydrate, hydrochloride.

The reaction should preferably be carried out in excess of piperidone-hydrate hydrochloride. Preferably more than 1.5 equivalents of 4-piperidone pr equivalent 5-chloro-1-(4-fluorophenyl)indole, more preferably more than 1.75, are used. Conveniently, 2.0 equivalents are used.

It is important that sufficient acid is present to allow a sufficient yield. When hydrochloric acid is used as mineral acid, it is preferably used in an amount of at least 2.5 mL concentrated HCl pr. g 5-chloro-1-(4-fluorophenyl)indole. Most preferably the ratio is 3.5 to 5 mL concentrated HCl pr. g 5-chloro-1-(4-fluorophenyl)indole.

The amount of acetic acid has to be sufficient to make the reaction technically feasible. Conveniently, at least 8 mL acetic acid pr. g 5-chloro-1-(4-fluorophenyl)indole is used. Preferably, the amount of acetic acid is more than 10 mL acetic acid pr. g 5-chloro-1-(4-

fluorophenyl)indole, most preferably 10 - 14 mL. The ratio between acetic acid and concentrated HCl is preferably 2:1 to 4:1 vol/vol.

The reaction is conveniently carried out by adding, drop-wise, a solution of the 5-chloro-1-(4-fluorophenyl)indole in hot acetic acid to the piperidone-hydrate, hydrochloride or by mixing the two reactants in a mixture of acetic acid and mineral acid followed by reflux. The reaction time is easily determined by a person skilled in the art.

The intermediate may be worked up in a conventional manner.

The further process leading to sertindole comprises cyclization of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine to the corresponding 3-acetoxy-indole using *eg.* acetic anhydride in the presence of alkalimetal acetate such as sodium acetate. 5-chloro-1-(4-fluoro)indole is then obtained from the 3-acetoxy-indole by reduction and subsequent elimination of $H_2O$. The resulting 5-chloro-1-(4-fluorophenyl)indole is reacted with 4-piperidone according to the above procedure, the resulting 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole is reduced in order to obtain 5-chloro-1-(4-fluorophenyl)-3-(piperidin-4-yl)indole which in turn is reacted with 1-(2-chloroethyl)-2-imidazolidinon to obtain sertindole. Alternatively, the 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole may first be reacted with 1-(2-chloroethyl)-2-imidazolidinon followed by reduction, thereby obtaining sertindole, which may be isolated as an acid addition salt, e.g. the tartrate, or as the free base.

The alkalimetal salt of 2,5-dichlorobenzoic acid and the alkalimetal salt of N-(4-fluorophenyl)glycine used as starting materials are easily prepared from commercially available 2,5-dichlorobenzoic acid and N-(4-fluorophenyl)glycine, respectively, by standard procedures.

Sertindole, as obtained by the process, may conveniently be formulated as described in US patent No 5,112,838.

**Experimental Section**

**Example 1**

**Preparation of N-(4-fluorophenyl)-N-(2-carboxyphenyl)glycin**

A suspension comprising potassium 2,5-dichlorobenzoate (100 g, 0.44 mol, 1 eq.), potassium N-(4-fluorophenyl)glycinate (190 g, 0.92 mol, 2.1 eq.), potassium carbonate (36.2 g, 0.26 mol, 0.6 eq. $CO_3^{--}$), copper bronze (2.8 g, 0.04 mol Cu, 0.1 eq.) and 250 mL demineralised water was heated at reflux under $N_2$ atmosphere for 20.5 hours and then cooled to 50 °C.

2.5 mL water and 5 g activated carbon were added to the reaction mixture which, except for the Cu-bronze, was homogeneous. The mixture was allowed to cool under stirring for 1 hour and filtered. The filter cake was washed with 2 x 125 mL water. The filtrate was poured on a mixture of ice (2 L) and 37% aq. HCl (3-400 mL) under vigorous stirring, thereby crystallising the crude product as a fine, crystalline, yellow-brown material. The suspension was stirred at 75-80 °C for 30 min, cooled to 15-20 °C, and filtered, and the filter cake was washed with 500 mL water and dried under air stream over night at 50 °C. The filtrate was collected for regeneration of N-(4-fluorophenyl)glycinate.

Yield of crude product: 113 g (80.3%), mp. 170-86 °C.

HPLC-analysis: 84.2% w/w product, 10.5% w/w 3-chlorosalicylic acid.

20 g of the above dry crude product was further purified by suspension in 200 mL toluene and reflux for 30 min. The suspension was allowed to cool to room temperature under stirring and was then filtered. The filter cake was washed with toluene (20 mL) and dried overnight in vacuum at 50 °C.

Yield: 17.0 g, mp. 190-92 °C. Purity > 98% as determined by NMR-analysis.

**Example 2**

**Preparation of N-(4-fluorophenyl)-N-(2-carboxyphenyl)glycin**

21.0 kg potassium 2,5-dichlorobenzoate was added to a 180 L reactor and 36.0 L water was added. This mixture was heated under stirring until substantially all solids were dissolved

(temp 60 - 70 °C) and 25.0 kg potassium N-(4-fluorophenyl)glycinate was added slowly. The mixture was heated until all materials were dissolved, i.e. at about 80 °C and added to a mixture of 7.67 kg $K_2CO_3$ , 582 g Cu-bronze and 7 L water. The combined mixture was refluxed overnight (about 15 h) and cooled to 50 °C. 1 kg activated carbon suspended in 5 L water was added followed by 40 L water. The mixture was stirred under cooling for 1 hour, and filtered on a nutch covered with filter aid. The filter cake was washed with 10 L water and the green filtrate was slowly during about 2 hours poured on a mixture of 22.5 L 37% HCl and 30 L water under gentle heating (45 - 50 °C) and stirring. The mixture was heated to 72 °C, cooled to 25 °C and filtered. The filter cake was washed with water (2 x 10 L) and dried on trays overnight at 60 °C. Yield 26.7 kg of a pale yellow crystalline crude product.

The crude product, 26.7 kg, was transferred to a 200 L reactor and 150 L toluene added and the mixture was heated to the reflux temperature (90 °C) under $N_2$ cover. Then the mixture was destilled until a temperature of 110 °C was reached (5 L distillate). 5 L toluene was added, and the mixture was refluxed at 110 °C for 2 hours, cooled to about 60 °C and left overnight at 27 °C. The mixture was filtered and the filter cake was washed with toluene (3 x 15 L) and dried, thereby obtaining 21.0 kg of the pure title product.

**Example 3**

**1-(4-flourophenyl)-3-acetoxy-5-chloroindole**

N-(4-flourophenyl)-N-(2-carboxyphenyl)glycin (717.1 g, 2.22 mol), sodium acetate (36.4 g, 0.44 mol, 0.2 eq.) and acetic anhydride were placed in a 4 L three necked flash equipped with mechanical stirrer and reflux condenser.

The suspension was heated under stirring until reflux. The reaction mixture was refluxed for 1 hour and was cooled to room temperature on ice/water bath. The homogenous suspension was under stirring poured onto ice (2 L) and was neutralised with concentrated NaOH (appr. 6 L) until a pH of 6-7. During the neutralisation the temperature was kept under appr. 30 °C, which required the adding of a further 5-6 L of ice. Thereby the product precipitated and was

isolated by filtration. The product was washed thoroughly with 3 L of water and 2 L of n-Heptane and dried over night in vacuum at 60 °C.
Yield: 600.5 g (89.1%), mp 109-12 °C.

**Example 4**

**1-(4-fluorophenyl)-5-chloroindole**

1-(4-flourophenyl)-3-acetoxy-5-chloroindole (100.0 g, 0.33 mol) was dissolved in 1000 mL EtOH. During the next hour sodium borohydride pellets (18.7 g, 1.5 eq.) were added batchwise at reflux. The reaction mixture was stirred over night at reflux and cooled to room temperature. Concentrated HCl (appr. 50 mL until pH 1) was added and the reaction mixture was stirred at room temperature for 1 hour. 200 mL demineralized water was added, and the resulting suspension was filtrated. The filter cake was washed with further 50 mL water and 10 mL EtOH. The product was dried over night in vacuum at 50 °C.
Yield: 68.4 g (84.7%), mp 91-93 °C.

**Example 5**

**Preparation of 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole**

5-chloro-1-(4-fluorophenyl)indole (6.70 kg) and 4-piperidone-mono-hydrate,hydrochloride (8.38 kg) were transferred to a 200 L reactor under $N_2$ cover. Acetic acid (67 L) was added and the reaction mixture was heated to 60°C. Concentrated HCl (37%, 33.5 L) was added during 1/2 hour and then the mixture was heated to the reflux temperature (85°C) and refluxed for 1 hour (final temperature 95°C). After cooling to 30°C, 33.5 L acetone was added followed by further cooling to 25°C. Filtration, wash (acetone 20 L) and drying in vacuum at 60°C gave the title product as a white powder, yield 8.94 kg.

**Example 6**

**1-[2-[4-[5-chloro-1-(4-flourophenyl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolidinone**

5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole (6.0 kg. 16.5 mol), 1-(2-chloroethyl)imidazolon (3.19 kg, 1.3 eq.), sodium carbonate (anhydrous) and methyl isobutyl ketone (60 L) were mixed. The reaction mixture was heated under $N_2$-cover and stirring until 90-95 °C, and was stirred over night at this temperature. The next day the reaction mixture was filtered while still hot. The apparatus and filter cake were washed with futher 2.5 L of methyl isobutyl ketone. The combined filtrates were left over night for crystallisation. The product was isolated on a nutch, washed with 7.5 L n-Heptane and dried over night in vacuum at 60 °C.

Yield: 5.39 kg (74.3%), mp 146.4 °C.

**Example 7**

**1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1-*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone, tartrate**

1-[2-[4-[5-chloro-1-(4-flourophenyl)-1H-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolidinone (3.5 kg) was dissolved in acetic acid (98-100%, 29 L) while being heated until 40 °C. Activated carbon was added and the suspension was stirred for 1 hour, left over night and filtered. The filter cake was washed with 6 L acetic acid. The combined filtrates were added to a 50 L hydrogeneration reactor which was covered by $N_2$. 70 g $PtO_2$ was added, the apparatus was closed and $N_2$ blown through for 5 min. Hydrogeneration was carried out in an $H_2$-flow (2.5 L per min) for 8.25 H.

The reaction mixture was blown through with nitrogen, activated carbon was added and the mixture was filtered on a closed nutch. The filtrate was combined with corresponding filtrates of three other hydrogenerations (a total of 14.53 kg starting material) and evaporated in vacuum at appr. 50 °C. The filtrate was flushed off with 3 x 10 L toluene at 50-60 °C. The remanence was dissolved in 146 L ethanol and to this suspension a 40 °C suspension of 5.22 kg L -(+) tartaric acid in 16 L demineralised water was added under stirring. The suspension

was left over night with no cooling or stirring. The crystallised tartrate was filtered on a nutch and washed with 15 L ethanol.

The crude tartrate was recrystallised from 190 L ethanol and 30 L demineralised water by heating until boiling (appr. 78 °C). The suspension was left over night for crystallasation with no cooling or stirring. The next day the suspension was cooled to appr. 18 °C and the tartrate was filtered off, washed with 60 L ethanol and dried over night under air stream at 60 °C.

**Example 8**

**1-[2-[4-[5-chloro-1-(4-flourophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone**

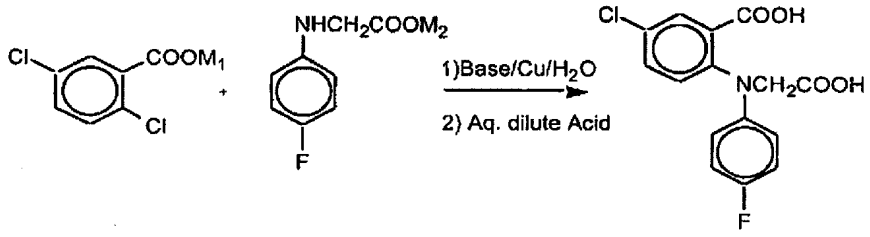
7.96 kg 1-[2-[4-[5-chloro-1-(4-flourophenyl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolodione, tartrate was suspended in 25 L demineralised water and 30 L dichloromethane was added. A total of 3 L 27% NaOH-solution, pH=9, was added to the suspension under stirring. The mixture was stirred for 1 hour (pH still =9), whereafter the dichloromethane phase was separated.

The water phase was extracted with further 15 L dichloromethane. The combined dichloromethane phases were dried with $NaSO_4$ and were evaporated.The product was flushed off with 5 L acetone, 35 L acetone was added and the suspension was heated until reflux. The crystallised product did not dissolve completely. Heating was discontinued and the mixture was left over night with gentle cooling. The crystallised product was isolated on a nutch, washed with further 5 L acetone and dried over night under air stream at 60 °C.

Yield: 4.90 kg (83.2%), mp 154.7 °C.

## CLAIMS

1. A process for the preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophe-nyl)-glycine comprising a copper catalysed arylation of 2,5-dichlorobenzoic acid with N-(4-fluorophenyl)glycine in which alkalimetal salts of 2,5-dichlorobenzoic acid and N-(4-fluorophenyl)glycine are employed in an aqueous, alkaline environment in the presence of a copper catalyst according to the reaction scheme:




wherein $M_1$ and $M_2$ are alkali metal ions.

2. A process according to Claim 1, **characterised in** that the reaction is carried out at an elevated temperature, preferably at a temperature between 80 °C and the reflux temperature of the medium, in particular at about the reflux temperature.

3. A process according to Claim 1 or 2, **characterised in** that the reaction medium is water or water to which a cosolvent is added.

4. A process according to Claim 3, **characterised in** that water is used as solvent.

5. A process according to Claim 3 or 4, **characterised in** the amount of water is less than 10 mL/g 2,5-dichlorobenzoic acid, preferably less than 5 mL/g

6. A process according to Claim 5, **characterised in** the amount of water is less than 3.5 mL/g, preferably less than 2.5 mL/g 2,5-dichlorobenzoic acid.

7. A process according to any of Claims 1 to 6, **characterised in** that the alkalimetal salts used are the lithium, sodium or potassium salts.

8. A process according to Claim 7, **characterised in** that the same salt of the reactants are used, preferably the potassium salts.

9. A process according to any of Claims 1 to 8, **characterised in** that the base is an alkalimetal carbonate, preferably $Li_2CO_3$, $Na_2CO_3$ or $K_2CO_3$.

10. A process according to any of Claim 9, **characterised in** that the alkalimetal of the alkali metal carbonate is the same as the alkalimetal of the reactants.

11. A process according to any of Claims 1 to 8 **characterised in** that the base is potassium carbonate.

12. A process according to any of Claims 1 to 11 **characterised in** that the amount of base is larger than the stoechiometric amount of 2,5-dichlorobenzoic acid.

13. A process according to any of Claims 1 to 12 **characterised in** that the catalyst is copper-bronze.

14. A process according to any of Claims 1 to 13 **characterised in** that the ratio between the amounts of the alkalimetal salt of N-(4-fluorophenyl)glycine and the alkali metal salt of 2,5-dichlorobenzoic acid is from 0.5 to 3.0, preferably 1.0 to 2.5, in particular 2.0 to 2.3 mol/mol.

15. A process for preparing 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole comprising reaction of 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone in a mixture of a mineral acid and acetic acid.

16. Process according to Claim 15, **characterised in** that the 4-piperidone is used in the form of 4-piperidone-hydrate,hydrochloride.

17. Process according to Claim 15 or 16, **characterised in** that the mineral acid used is phosphoric acid, nitric acid, sulfuric acid or hydrochloric acid.

18. Process according to Claim 17, **characterised in** that the mineral acid used is concentrated hydrochloric acid.

19. Process according to Claim 15 or 16, **characterised in** that at least 1.5 equivalents of 4-piperidone is used pr. equivalent 5-chloro-1-(4-fluorophenyl)indole.

20. Process according to Claim 19, **characterised in** that at least 1.75 equivalents of 4-piperidone is used pr. equivalent 5-chloro-1-(4-fluorophenyl)indole.

21. Process according to Claim 20, **characterised in** that at least 2.0 equivalents of 4-piperidone is used pr. equivalent 5-chloro-1-(4-fluorophenyl)indole.

22. Process according to Claim 18, **characterised in** that hydrochloric acid is used in an amount of at least 2.5 mL concentrated HCl pr. g 5-chloro-1-(4-fluorophenyl)indole.

23. Process according to Claim 15 or 16, **characterised in** that at least 8 mL acetic acid pr. g 5-chloro-1-(4-fluorophenyl)indole is used.

24. Process according to Claim 23, **characterised in** that at least 10 mL acetic acid is used pr. g 5-chloro-1-(4-fluorophenyl)indole.

25. Process according to Claim 24, **characterised in** that 10 - 14 mL acetic acid is used pr. g 5-chloro-1-(4-fluorophenyl)indole.

26. Process according to Claim 22, **characterised in** that the ratio is 3.5 to 5 mL concentrated HCl pr. g 5-chloro-1-(4-fluorophenyl)indole.

27. Process according to Claim 18, **characterised in** that the ratio between acetic acid and concentrated HCl is 2:1 to 4:1 (vol/vol).

28. A process of manufacturing sertindole comprising preparation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine by a process of any of Claims 1 to 14, and/or preparation of 5-chloro-1-(4-flourophenyl)-3-(1,2,3,6-terohydropyridine-4-yl)indole according to any of claims 15-27.

29. A process of manufacturing sertindole comprising

a) preparation according to any of claims 1-14 of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine, by reacting an alkalimetal salt of 2,5-dichlorobenzoic acid with an alkalimetal salt of N-(4-fluorophenyl)glycine in an aqueous, alkaline environment in the presence of a copper catalyst;

b) cyclisation of N-(4-fluorophenyl)-N-(2-carboxy-4-chlorophenyl)glycine to the corresponding 3-acetoxy-indole using acetic anhydride/alkalimetal acetate, preferably sodium acetate

c) reduction of the 3-acetoxy-indole and subsequent

d) elimination of $H_2O$ thereby obtaining 5-chloro-1-(4-fluorophenyl)indole

e) reaction of 5-chloro-1-(4-fluorophenyl)indole with 4-piperidone according to any of claims 15-27 in a mixture of an acetic acid and concentrated HCl

f) reduction of the resulting 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole in order to obtain 5-chloro-1-(4-fluorophenyl)-3-(piperidin-4-yl)indole

g) reaction of the product of f) with 1-(2-chloroethyl)-2-imidazolidinon, or

h) reaction of 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)indole with 1-(2-chloroethyl)-2-imidazolidinon followed by reduction of the product, thereby obtaining sertindole.